APPENDIX B

1. (Once Amended) Use of a composition ~~containing~~**comprising** substances contained in *Cimicifuga Racemosa* extract, or derivatives thereof, which induces a physiological estrogen-like effect without interacting with breast cancer cells, ~~in particular without stimulating breast cancer cells,~~ for the preparation of a medicament for the treatment of **an** estrogen deficiency ~~symptoms~~**symptom** or ~~diseases~~**disease** of a mammal suffering from or having a high risk of developing breast cancer.

3. (Once Amended) Use according to ~~any of the preceding claims,~~**claim 1,** wherein the physiological estrogen-like effect is uterine growth as determined by an increase in uterine weight compared to controls after administration of the composition to ovariectomized female athymic nude mice.

4. (Once Amended) Use according to ~~any of the preceding claims,~~**claim 1,** wherein the physiological estrogen-like effect is uterine growth as determined by an increase in mean uterine weight compared to controls of at least 0.10 g after administration of the composition to ovariectomized NMRI female athymic nude mice for 8 days.

5. (Once Amended) Use according to ~~any of~~ claims 3 or 4, wherein the increase in uterine weight obtained by administration of a dose comparable to a normal dose for the mammal to be treated of the composition corresponds to a weight increase obtainable in the same test animal by estradiol treatment.

7. (Once Amended) Use according to ~~any of the preceding claims,~~**claim 1,** wherein the physiological estrogen-like effect is a change in gonadotropins (FSH and/or LH) as determined by available validated radioimmuno assay techniques.

8. (Once Amended) Use according to ~~any of the preceding claims,~~**claim 1,** wherein the physiological estrogen-like effect is a change in cytology of the vaginal cells as determined by cytological counts.

9. (Once Amended) Use according to ~~any of the preceding claims,~~**claim 1,** wherein the composition ~~do~~**does** not interact~~, in particular stimulate,~~ **with** cancer cells that are estrogen receptor-negative.

10. (Once Amended) Use according to ~~any of the preceding claims,~~**claim 1,** wherein the lack of ~~stimulation~~**interaction** ~~of~~**with** breast cancer cells is determined by no effect of the composition **as** compared to a control on growth of the estrogen and progesterone receptor negative MDA-MB-231 (ATCC HTB-26) human breast cancer cell line inoculated into six-week-old female athymic nude mice determined when control tumours show increasing size during at least six consecutive growth ~~recordings~~**recordings**.

11. (Once Amended) Use according to ~~any of the preceding claims,~~**claim 1,** wherein the composition ~~do~~**does** not interact~~, in particular stimulate,~~ **with** cancer cells that are estrogen receptor-positive.

12. (Once Amended) Use according to ~~any of the preceding claims,~~**claim 1,** wherein the lack of ~~stimulation~~**interaction** ~~of~~**with** breast cancer cells is determined by no effect of the composition compared to a control on growth of the estrogen dependent and estrogen receptor-positive MCF-7 (ATCC HTB-22) human breast cancer cell line inoculated into six-week-old female athymic nude mice determined when control tumours show increasing size during at least six consecutive growth recordings.

13. (Once Amended) Use according to ~~any of the preceding claims,~~**claim 1,** wherein the lack of ~~stimulation~~**interaction** ~~of~~**with** breast cancer cells is determined by no effect of the composition when given in combination with estradiol compared to a control on growth of the estrogen dependent and estrogen receptor-positive MCF-7 (ATCC HTB-22) human breast cancer cell line inoculated into six-week-old female athymic nude mice determined when control tumours show increasing size during at least six consecutive growth recordings.

14. (Once Amended) Use according to ~~any of the preceding claims~~**claim 1** for the treatment of estrogen deficiency symptoms or diseases of humans having breast cancer, having a high risk of recurrent breast cancer, or having a risk ~~(such as high risk)~~ of developing breast cancer.

15. (Once Amended) Use according ~~to any of the preceding claims,~~**claim 1,** wherein the estrogen deficiency-~~conditioned~~ symptom or disease **includes** ~~is selected from the group consisting of~~ **a** menopausal ~~symptoms~~**symptom**; **a** dermatological ~~disorders such as ageing of the skin, wrinkles, dry skin and other estrogen deficiency related dermatological disorders~~**disorder**; dryness of mucous membranes ~~(e.g. vaginal and intestine)~~; **a** brain related disease ~~such as Alzheimer's including other types of dementia~~; **a** bone ~~and~~**or** joint related ~~diseases such as osteoporosis, osteochondrosis, osteoarthritis, rheumatoid arthritis, healing of bone fractures, and reduction in skeletal fractures~~**disease**; vaginal estrogen deficiency ~~such as vaginal dryness and dyspareuni~~; **a** coronary heart ~~diseases such as arteriosclerosis; and~~ disease ~~such as~~**;** hyperlipidaemia and ~~hypercholesterolaemia~~**hyper-cholesterolaemia**.

16. (Once Amended) Use according to ~~any of the preceding claims,~~**claim 1,** wherein the estrogen deficiency-~~conditions symptoms are~~ **symptom is a** menopausal symptom~~s~~.

17. (Once Amended) Use according to ~~any of the preceding claims,~~**claim 1,** wherein the composition is or ~~contains~~**includes** *Cimicifuga Racemosa* extract.

18. (Once Amended) Use according to ~~any of the preceding claims,~~**claim 1,** wherein the composition is a composition comprising *Cimicifuga Racemosa* plant parts.

19. (Once Amended) Use according to ~~any of the preceding claims,~~**claim 1,** wherein the composition is a composition comprising SPP-001.

20. (Once Amended) Use according to ~~any of the preceding claims,~~**claim 1,** wherein the composition is a composition ~~containing~~**comprising** one or more chemical compounds contained in *Cimicifuga Racemosa* extract, or derivatives thereof.

21. (Once Amended) Use according to ~~any of the preceding claims,~~**claim 1,** wherein the composition is combined with a drug which has a selective estrogen receptor modulating (SERM) ~~actitivty~~**activity**.

22. (Once Amended) A container comprising a composition according to ~~any of the preceding claims~~**claim 1** with a ~~pharmaceutically~~**pharmaceutical** carrier and comprising an

indication for relief of **an** estrogen deficiency ~~symptoms~~**symptom** without increasing the risk of developing or worsening estrogen dependent cancer.

23. (Once Amended) A container comprising a composition which induces a physiological estrogen-like effect without stimulating breast cancer cells ~~with~~, a ~~pharmaceutically~~**pharmaceutical** carrier and **further** comprising an indication for relief of estrogen deficiency symptoms without increasing the risk of developing or worsening estrogen dependent cancer.

24. (Once Amended) A method for relieving symptoms caused by estrogen deficiency in a mammal suffering from or having a high risk of developing an estrogen dependent tumour comprising administering to the mammal a composition ~~containing~~**comprising** substances contained in *Cimicifuga Racemosa* extract, or derivatives thereof, which induces a physiological estrogen-like effect without stimulating breast cancer cells.

25. (Once Amended) A method according to ~~the previous~~ claim~~,~~ **24,** wherein the mammal is a human.

26. (Once Amended) A method for screening for substances or compositions which can be used according to claim 1 or 2, comprising subjecting ~~test~~ substances or compositions to

1. testing for possible estrogen-like effect in normal tissue by measuring increase in uterine weight, changes in gonadotropins, changes in vaginal cytology ~~and/or~~, postmenopausal symptoms **or a combination thereof** in an adult female mammal, and

2. testing for possible estrogenic effect in breast cancer, and selecting, as candidates for tissue-selective estrogenic substances or compositions useful in the method ~~according~~**according** to claim 1 or 2, substances or compositions which,

a) are capable of inducing physiological estrogenic effects in female mammals, and at the same time

b) have no effect on the growth of estrogen receptor-negative cancer cells and no effect on estrogen receptor-positive cancer cells in the doses in which they induce physiological estrogen effects.

27. (Once Amended) A method according to claim 26, wherein the capability of the substance or ~~compositioncomposition~~ of inducing physiological estrogen effects ~~e.g. uterine growth female mammals~~ is tested by testing the capability of the substance or composition of effecting uterine weight increase in ovariectomized female NMRI athymic nude mice, the lack of effect of the substance or composition on the growth of estrogen receptor-negative cancer cells is assessed as the lack of capability of the substance or composition of supporting growth of MDA-MB231 xenografts in female NMRI athymic nude mice, and the lack of effect of the substance or composition on the growth of estrogen receptor-positive cancer cells is assessed as the lack of capability of the substance or composition of supporting growth of MCF-7 (ATCC (HTB-22) xenografts in female NMRI athymic nude mice.

28. (Once Amended) A method for relieving or curing symptoms or diseases which are caused by estrogen deficiency, or which can be relieved or cured by administration of steroidal estrogen, in a mammal who suffers from breast cancer, or has a risk of recurrent breast cancer, or has a high risk of developing breast cancer, the method comprising administering, to the mammal, a composition which has an estrogen-like effect, as evidenced by a capability of the composition of ~~inducing~~**inducing** physiological estrogenic effects in adult mammal, and which is free from interaction with breast cancer cells, ~~in particular free from a stimulating effect on breast cancer,~~ thereby treating estrogen deficiency symptoms or diseases without introducing a risk of provoking the development of clinically evident breast cancer, ~~and/or~~ stimulating growth of existing breast cancer cells in the mammal **or a combination thereof**.

29. (Once Amended) A method according to claim 28, wherein the mammal is **a** female mammal.

31. (Once Amended) A method according to ~~any of claims 29-30,~~**claim 29,** wherein the estrogen-like effect possessed by the composition manifests itself in the composition being

capable of inducing an increase in uterine weight in adult ovariectomized NMRI female athymic nude mice.

34. (Once Amended) A method according to ~~any of claims 28-33,~~**claim 28,** wherein the estrogen-like effect possessed by the composition manifests itself in the composition being capable of inducing a lowering in FSH and LH in females.

36. (Once Amended) A method according to ~~any of claims 28-35,~~**claim 28,** wherein the composition is one which has no effect on the growth of estrogen receptor-negative cancer cells.

38. (Once Amended) A method according to ~~any of claims 28-37,~~**claim 28,** wherein the composition is one which is free from any effect on breast cancer cells even where the breast cancer cells are documented as being estrogen receptor-positive.

39. (Once Amended) A method according to ~~any of claims 28-38,~~**claim 28,** wherein the composition is one which has substantially no agonizing and substantially no antagonizing effect on the effect of ~~estrogen such as estradiol~~**estrogen** on breast cancer cells, even where the breast cancer cells are documented as being estrogen receptor-positive.

41. (Once Amended) A method according to ~~any of claims 38-40,~~**claim 38,** wherein the composition is one which has no effect on xenografts of the estrogen receptor-positive and estrogen dependent MCF-7 (ATCC HTB-22) human breast cancer cell line in nude mice, as evidenced by the composition having no growth supportive effect and no growth inhibitory effect on the xenografts whether given alone or in combination with estradiol.

42. (Once Amended) A method according to claim 41, wherein the composition is one which has no effect on xenografts of the estrogen receptor-positive and estrogen dependent MCF-7 (ATCC HTB-22) human breast cancer cell line in nude mice, as evidenced by the composition having no growth supportive effect and no growth inhibitory effect on the xenografts whether given alone or in combination with estradiol, even where the composition is ~~administered~~**administered** in a dose which is 10 ~~or even 100~~ times higher than a dose giving, in the same strain of nude mice, a maximum uterus weight increase.

43. **(Once Amended)** A method according to ~~any of claims 28-42,~~**claim 28,** wherein the estrogen deficiency-conditioned symptom or disease **includes** ~~is selected from the group consisting of~~ **a** menopausal ~~symptoms~~**symptom, a** dermatological ~~disorders such as ageing of the skin~~**disorder**, ~~dryness of mucous membranes (e.g. vaginal and intestine),~~**a** brain related disease ~~such as Alzheimer's including other types of dementia,~~ **a** bone and joint related disease ~~such as osteoporosis, osteochondrosis, osteoarthritis, rheumatoid arthritis, healing of bone fractures, and reduce in skeletal fractures and disease such as~~ hyperlipidaemia, hypercholesterolaemia, **and** arteriosclerosis.

44. (Once Amended) A method according to claim 43, wherein the estrogen deficiency-~~conditions symptoms~~**conditioned symptoms** are menopausal symptoms.

45. (Once Amended) A method according to ~~any of~~ claims 28-~~44,~~ **or 43,** wherein the composition is a composition ~~containing~~**comprising** substances ~~contained~~**included** in *Cimicifuga Racemosa* extract, or derivatives thereof.

46. (Once Amended) A method according to claim 45, wherein the composition is or ~~contains~~**includes a** *Cimicifuga Racemosa* extract.

49. (Once Amended) A method according to claim ~~45,~~**46,** wherein the composition is a composition comprising ~~*Cimicifuga Racemosa* plant parts.~~one or more chemical compounds ~~contained~~**included** in ~~*Cimicifuga Racemosa*~~***Cimicifuga Racemosa*** extract, or ~~derivatives~~**derivatives** thereof.

51. (New) Use according to claim 1, wherein the composition induces a physiological estrogen-like effect without stimulating breast cancer cells.

52. (New) Use according to claim 9, wherein the composition does not stimulate cancer cells that are estrogen receptor-negative.

53. (New) Use according to claim 10, wherein the lack of interaction with breast cancer cells is lack of stimulation of breast cancer cells.

54. (New) Use according to claim 11, wherein the composition does not stimulate cancer cells that are estrogen receptor-positive.

55. (New) Use according to claim 12, wherein the lack of interaction is lack of stimulation of breast cancer cells.

56. (New) Use according to claim 13, wherein the lack of interaction is lack of stimulation of breast cancer cells.

57. (New) A method according to claim 28, wherein the composition is free from a stimulating effect on breast cancer.

58. (New) A method according to claim 39, wherein the composition has substantially no agonizing and substantially no antagonizing effect on the effect of estradiol on breast cancer cells.